MYOCARDIAL INFARCTION IN SICKLE CELL DISEASE

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Gross and microscopic findings consistent with acute (three patients) and healed (four patients) myocardial infarction were found in seven (9.7%) of 72 consecutive hearts from patients with sickle cell disease studied after autopsy between 1950 and 1982. Gross obstructive and atherosclerotic lesions were absent in all seven patients, while microthrombi were present in the arterioles of infarcted tissue in two patients. Pathophysiological mechanisms responsible for the infarction are unclear, but anemia, platelet thrombi, coronary vasospasm, and abnormal rheology related to sickle cells may all be important. Chest pain occurred clinically in six of the seven patients and ECG findings typical of infarction were found in two patients. One patient died suddenly. These findings suggest that ischemic heart disease may be present in a significant number of patients with sickle cell disease and should be considered in all patients who complain of chest pain, whether or not the patient is in crisis. (*J Natl Med Assoc.* 1996;88:428-432.)

Key words • myocardial infarction • sickle cell disease

Although cardiac findings are prominent clinical features of sickle cell anemia and its variants, ventricular dysfunction due to vascular obstruction by aggregates of sickled erythrocytes has been postulated but infrequently found.[1,2] Acute cor pulmonale has been previously described.[3] A fatal case of acute myocardial infarction with typical pathological features in a young female with sickle cell disease has been separately reported by us.[4] In this report, we describe the clinical and pathological features of seven patients with sickle cell disease who had either acute, healed, or a combination of pathological lesions consistent with ischemic injury without associated atherosclerosis, documented at autopsy.

MATERIALS AND METHODS

Gross anatomical and histological evidence of myocardial lesions was reviewed in 72 consecutive autopsies performed on patients with sickle cell disease at the LAC+USC Medical Center between 1950 and 1982.[5] The hemoglobinopathy diagnosis was established during life in these patients by hemoglobin electrophoresis on cellulose acetate and confirmed by citrate agar gel electrophoresis. In one patient (Table 1, #4), the diagnosis of sickle cell anemia (HbSS) was based on the clinical description of a chronic hemolytic anemia with sickled erythrocytes on blood smear, intermittent bone pain, cholelithiasis, and pathologic evidence of auto-infarction of the spleen.[2]

All autopsies were performed under the supervision of, and the pathological material reviewed by, one of us (D.T.) as senior pathologist of the autopsy service. Subsequently, a secondary review of all available material was carried out in preparation of this report. In the initial examination, the coronary arteries were examined grossly in their anatomical position for evidence of thrombosis or gross atherosclerotic lesions. The vessels were then serially cross-sectioned at approximately 3- to 4-mm intervals and inspected antigrade and retrograde for obstructive lesions. Special care was taken at bifurcations and sites of common atherosclerotic obstruction and serial sections made. After gross inspection for obvious lesion or scar formation, serial

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TABLE 1. DEMOGRAPHIC, LABORATORY, AND CAUSE OF DEATH FINDINGS IN PATIENTS WITH SICKLE CELL ANEMIA

Patient No.	Age (Years)	Sex	Hb	Heart Weight (g)	LV*	RV*	Cause of Death
1	68	M	SC	450	13	2	Fat emboli
2	33	M	SS	470	13	4	Sudden death (? arrhythmia)
3	63	M	SS	540	17	6	Virus-associated hemophagocytic syndrome
4	25	F	SS	320	12	3	Acute myocardial infarction
5	51	M	SS	420	17	3	Sepsis
6	44	F	SC	580	14	3	Acute myocardial infarction, encephalomalacia
7	44	M	SS	540	15	5	Acute myocardial infarction and congestive heart failure
Means	47		474	14.4	3.7		

*Wall thickness in millimeters.

sections were made of the ventricles in bread-loaf fashion. When discrete lesions of any size were noted, sections were taken for fixing and paraffin block preparation. Standard hematoxylin and eosin staining was done and sections reviewed for discrete pathology. Myocardial infarction was considered when discrete lesions were present measuring one or more square centimeters in size. Cases with diffuse fibrotic streaking only were excluded from this report. Myocarditis was considered when a diffuse inflammatory or healed process was found.

The histological criteria for acute myocardial infarction consisted of coagulation necrosis with polymorphonuclear cell infiltration and replacement with granulation tissue. The criterion for healed infarction was dense myocardial replacement with fibrosis, and for healing (subacute) myocardial infarction, the criteria were discrete components of both granulation and fibrous tissue.

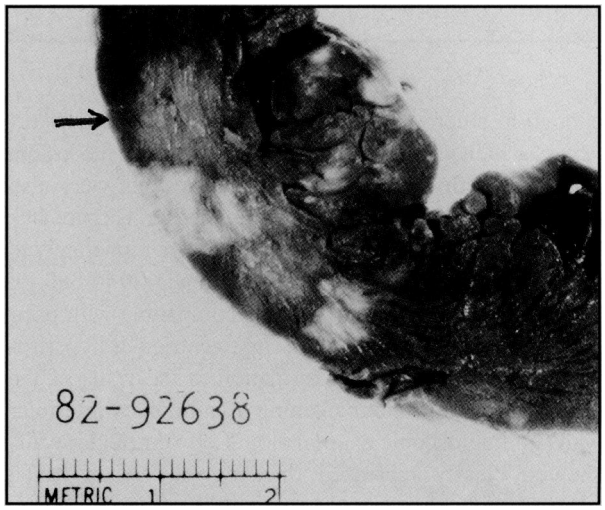

Figure 1. Cross section of the left ventricle of patient #6 (Table 2) stained with tetrazolium. Old and recent infarction is present; the old infarction areas are white and the acute infarction areas are pale (arrow).

RESULTS

Discrete localized lesions meeting the criteria described for myocardial infarction were found in seven of 72 patients (9.7%). Five of our patients were men and two were women (Table 1). Five patients had HbSS and two had HbSC. The mean age was 47 years (range: 25 to 68 years). There was a history of hypertension in only one case (#6). Other cardiac risk factors such as smoking, obesity, diabetes mellitus, and hypercholesterolemia were absent. The electrocardiograms of all patients were abnormal with changes typical of acute infarction in one and old infarction in one. The creatine kinase (CK) myocardial/brain fraction was elevated in one case and was not performed in the other six cases.

Three of seven patients had pathological changes consistent with acute myocardial infarction; one of these also had lesions consistent with healed infarction (Table 2, Figure 1). Four other patients had lesions consistent with healed or healing infarction of the left ventricle and two of these patients had findings typical of right ventricular infarction as well as left. No gross obstructive lesions of the major coronary arteries were found. Organized thrombi were found in three cases on microscopic examination in some coronary arterioles of the infarcted tissue.

In most cases, myocardial scars were in the proximity of, but not immediately adjacent to, discrete vessels. The absence of major obstructive lesions made specific correlations difficult. In some cases, the lesions were close

TABLE 2. ELECTROCARDIOGRAPHIC AND SPECIFIC CARDIAC FINDINGS AMONG 7 PATIENTS

Patient No.	EKG	Gross Description	Microscopic Findings
1	Nonspecific ST-T changes	Transmural fibrosis, left ventricle; 10% coronary atherosclerosis	Healed infarction
2	Left ventricular hypertrophy	Transmural fibrosis, left & right ventricles; no atherosclerosis	Healed infarction
3	Left ventricular hypertrophy, left atrial enlargement	Transmural fibrosis, left ventricle; 20% coronary atherosclerosis	Healing ischemic necrosis; organized microthrombosis
4	Acute inferior myocardial infarction	Pallor posterolateral left ventricle; no atherosclerosis	Acute transmural coagulation necrosis
5	None	Transmural fibrosis, left ventricle; no atherosclerosis	Healed infarction
6	Old inferior myocardial infarction; multifocal premature ventricular contractures	Transmural fibrosis, left ventricle, interventricular septum, right ventricle; no atherosclerosis	Acute coagulation necrosis, adjacent healed infarction; organized microthrombosis
7	Nonspecific ST-T changes	Transmural fibrosis, left ventricle; 20% coronary atherosclerosis	Localized acute coagulation necrosis (left ventricle, right ventricle, right atrium)

enough to a coronary vessel to surmise that flow disturbance in such vessel could have been related to the lesion. In the most florid instance, however, lesions were also present some distance from a discrete vessel (Figure 1).

The heart weights in these patients were moderately to markedly increased (mean: 474 g; range: 420 to 580 g). Three of the patients had findings compatible with prior pulmonary hypertension, with right ventricular hypertrophy and localized plaque formation in the walls of the pulmonary artery, and thickening of pulmonary arteriolar walls on microscopic examination. Left ventricular walls showed clearly increased thickness in six of seven patients, with 11 mm as the upper limit of normal.

DISCUSSION

In this study, myocardial infarction was found at autopsy in seven of 72 patients with sickle cell disease, a prevalence of 9.7% which has not been previously described. There have been several reports of myocardial scarring and degeneration in sickle cell disease, and healed myocardial infarction has been reported as an incidental finding in one patient with HbSC at autopsy.[3] Myocardial degeneration (not typical of acute or healed infarction) with organized coronary thrombi has been reported in one patient with sicklemia; however, this patient had no evidence of chronic hemolytic anemia and electrophoresis was not performed.[6] Curiously, in the largest previously study of cardiac pathology in sickle cell disease, no definitive evidence of acute or healed myocardial infarction was found in 52 cases.[2]

In the absence of significant coronary atherosclerosis, or major vessel obstruction, the cause of myocardial infarction is not obvious. In two acute cases, coronary thrombi were detected microscopically in some arterioles in the area of infarction and were thought to be possibly contributory as a mechanism of infarction. It is possible that thrombi were present in some of the small vessels of other cases but not present in tissue section selected for slide preparation. Nevertheless, several other mechanisms should be considered.

Vasospasm was postulated as a cause of organ infarction in sickle cell disease as early as 1948.[7] Several recent studies have found platelet survival to be decreasing during crises;[8-11] thromboxane, released from sequestered platelets in the coronary vasculature may play a role in myocardial ischemia and necrosis by inducing vasospasm. The rheological factors of altered viscosity membrane flexibility, and aggregation of the red blood cells in sickle cell disease could cause microcirculatory stasis[12,13] and may indeed act independently to cause coronary vascular obstruction leading to ischemia and infarction. As previously hypothesized,[14] myocardial hypoxia and resultant necrosis from anemia per se could have occurred in these patients; however, the mean hemoglobin in our seven patients were 8.6 + 1.8 g compared with 7.2+2.7 g in the other 65 patients.

Although intramyocardial sickling is rare in sickle cell disease (presumably due to rapid blood flow),[1] cor pulmonale with arterial hypoxemia could result in partially sickled cells entering the coronary circulation. The abnormal blood rheology in this disease may be accentuated resulting in vaso-occlusion, myocardial ischemia, and infarction.[13] An association between cor pulmonale and heart failure in sickle cell disease has

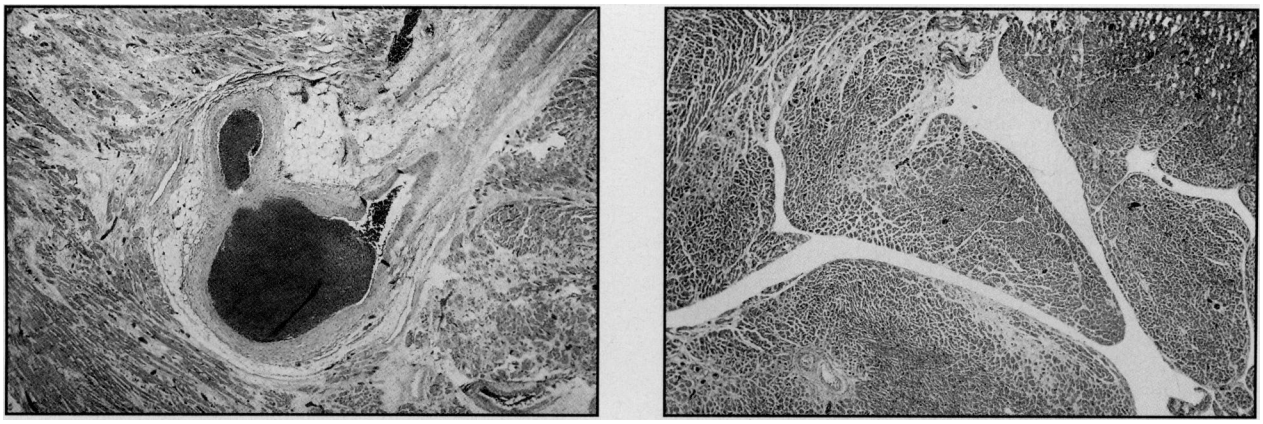

Figure 2. Microscopic specimens from patient #6. *Left:* This specimen shows acute infarction with coagulation necrosis clearly present. Note the presence of a thrombus in the arteriole near the center of the frame (magnification×16). *Right:* Chronic scar formation is indicated by the presence of replacement fibrosis.

been noted by others.[2,3] The occurrence of findings consistent with pulmonary hypertension in three of our patients raises questions regarding the significance of this association. Acidosis from renal failure and sepsis are other factors that may aggravate intracellular sickling and may unfavorably impact blood viscosity.

The average age of our sickle cell disease patients with myocardial infarction, 47 years, is substantially younger than the average age, 55 years, of African Americans with myocardial infarction in the presence of coronary artery disease. The younger age of patients in our series is typical of patients with myocardial infarction without atherosclerosis, although the true incidence of this entity in blacks in unknown.[15]

There are other important clinical implications of these findings. The diagnosis of myocardial infarction was entertained clinically in only three of the seven cases. There may be several explanations for this. The typical clinical and laboratory characteristics of myocardial infarction, such as chest pain and serum enzyme elevation, may be difficult to evaluate in sickle cell disease. Angina pectoris, although previously described in sickle cell disease,[16-18] is not usually considered because pain, regardless of location, is generally considered to be a manifestation of sickle cell crisis. The serum enzymes CPK, LDH and SGOT may not be helpful in the evaluation of myocardial infarction because these enzymes are frequently elevated on the basis of hemolysis or intramuscular injections. However, isoenzyme fractionation of CPK and classical electrocardiogram changes remain reliable for the diagnosis of myocardial infarction in the setting of sickle cell disease.[4,19]

A significant finding in this study was that of cardiac hypertrophy in all of the cases with infarction or major scar formation. In the absence of hypertension, the cause is not clearly evident, and it is possible that this represent 'work' hypertrophy in response to the hyperkinetics of chronic anemia and related hypoxia.

Our recently reported findings documenting the possibility of the clinical occurrence of acute myocardial ischemia,[19] and our findings and those of others documenting increased left ventricular filling pressure in sickle cell anemia are consistent with this hypothesis.[20-23]

The recent report by Berezowski, Mautner, and Roberts is clearly supportive of the frequent occurrence of myocardial scar formation as previously recorded by us.[5,24] Moreover, they report discrete myocardial infarction (healed) associated with atherosclerosis but no findings of myocardial necrosis. These authors attributed their findings to ischemia as do we; further, we believe that the "work of hypertrophy" so prevalent in both studies exaggerates the effect of the severe anemia.

Thus, acute myocardial ischemia and myocardial infarction should be seriously considered in all adults with sickle cell disease who complain of chest pain and should be considered a prime factor when sudden death occurs in patients with sickle cell disease. Whether there is a relationship between the cardiac findings noted here and the hemophagocytic syndrome or other pathophysiologic mechanisms remains to be explored.[25]

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